

### Remarks

The June 2, 2009, Official Action and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set forth in the June 2, 2009, Official Action. Therefore, the initial due date for response was September 2, 2009. A petition for a three (3) month extension of time is presented with this response, which is being filed within the one month extension period.

Turning to the substantive aspects of the June 2, 2009, Official Action, at page 2, the Examiner has maintained the rejection of claims 1, 2, 24, 28, 43 and 44 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. In accordance with the present amendment, claim 43 has been amended to indicate that production of Factor IX from the AAV vector in the mammal induces formation of inhibitory antibodies which are optionally determined by Bethesda titers. Support for this amendment can be found in original claim 12 as filed and throughout the specification. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §112, first paragraph rejection of claims 1, 2, 24, 28, 43-44, as set forth in the June 2, 2009 Official Action, cannot be maintained, and the rejection is respectfully traversed.

Before addressing the remaining rejection in this case, a review of the lengthy prosecution of this application is in order. While Applicants appreciate that the present Examiner has not been prosecuting this case since it was filed, 9 years

of prosecution cannot be ignored because the USPTO has assigned a new examiner to the case.

The filing date for this application is June 8, 2000. The claims as originally filed are set forth below.

1. A method of preventing the formation of inhibitory antibodies in a mammal undergoing gene therapy, said method comprising administering to said mammal an immunosuppressive agent in conjunction with said gene therapy.
2. The method of claim 1, wherein said mammal is a human.
3. The method of claim 1, wherein said gene therapy is delivery of a nucleic acid to said mammal, which when expressed in said mammal, serves to correct a genetic defect in said mammal.
4. The method of claim 3, wherein said protein is selected from the group consisting of Factor VII, Factor VIII, Factor IX, Factor X,  $\alpha$ 1- antitrypsinogen, glucuronidase, a sarcoglycan, an interferon, insulin-like growth factor, and erythropoietin.
5. The method of claim 4, wherein said gene therapy is delivery of Factor IX to said mammal.
6. The method of claim 1, wherein said gene therapy is performed by administering a viral vector to said mammal, wherein said viral vector comprises a nucleic acid to be delivered to said human.
7. The method of claim 6, wherein said viral vector is an adeno- associated viral vector.
8. The method of claim 5, wherein said Factor IX is delivered

to said mammal using an adeno-associated virus vector.

9. The claim 1, wherein said immunosuppressive agent is selected from the group consisting of cyclophosphamide, FK506, anti-CD40 ligand, CTLA4Ig, cyclosporin, antiB71-B72, and an immunosuppressive steroid.

10. The method of claim 9, wherein said immunosuppressive agent is cyclophosphamide.

11. The method of claim 9, wherein said immunosuppressive agent is FK506.

12. The method of claim 1, wherein said mammal has hemophilia B and said inhibitory antibodies specifically bind with Factor IX protein.

The first Official Action was dated November 8, 2001. In that Official Action, Examiner Whiteman characterized the subject matter enabled by the specification as follows:  
"...enabling for 1) A method of inhibiting the formation of inhibitory antibodies in a mammal undergoing gene therapy, said method comprising administering to said mammal, an immunosuppressive agent in conjunction with gene therapy; 2) the method of 1) wherein said gene therapy is performed by administered either an adeno-associated virus vector (AAV) or an adenovirus vector to said mammal; wherein said vector comprises a nucleic acid encoding allogenic Factor IX, wherein said immunosuppressive agent is cyclophosphamide. The claims were rejected as allegedly failing to enable vectors other than those cited above.

Notably, all of the claims were rejected under §102 as allegedly anticipated by Tengborn et al. (claims 1-5, 9, 10 and 12); Trapnell et al. (claims 1-6, 9-10 and 12)) and US

Patent 6,093,392. At the outset, Applicants note that in order to serve as an anticipatory reference under 35 U.S.C. §102, a reference must place the invention in the hands of the public. In other words, it must enable the claimed method.

In response to the Official Action, counsel for applicant argued that "the claimed methods do not require achieving a therapeutic benefit, rather only that the production of an inhibitory antibody to a protein delivered to a mammal via gene therapy be reduced or prevented". Indeed, the specification shows that administration of the immunosuppressive agent resulted in shorter aPTT times, a demonstrable response that was not observed in animals not receiving the immunosuppressive agent. Claim 1 was not amended to recite AAV or AV vectors or FIX and arguments were presented that distinguished the instant method over the art cited under §102.

In the second Official Action dated June 5, 2002, the Examiner maintained the §112, first paragraph rejection and raised a new rejection over US Patent 6,093,392 to High et al. in view of Smith et al. Examiner Whiteman again restated his position regarding what the specification enabled in this application. *"...because the specification while being enabling for 1) A method of preventing (or inhibiting) the formation of inhibitory antibodies to a Factor IX protein delivered to a mammal by way of gene therapy, wherein the method comprises:*

*a) administering cyclophosphamide (Cyp) multiple times to a mammal undergoing gene therapy, wherein the administration of cyp is administered at around the time the gene therapy is administered;*

*b) the gene therapy is delivery of Factor IX using an adeno-associated virus vector; and*

*c) the gene encoding the delivered Factor IX is from the same species as the mammal."* The Examiner also indicated that the aforementioned method using anti-CD40 ligand was enabled. As in the first official action, the §112, first paragraph

rejection was maintained because the claims encompassed other immunosuppressive agents and vector other than AAV. A telephonic interview with Examiner Whiteman was conducted on November 14, 2002 to discuss the art cited under \$103.

In the response filed on December 5, 2002, Applicants limited the claims to use of cyclophosphamide and anti-CD40 ligand. However, claim 1 still read on the use of any transgene and any vector. Applicants also referred to previously submitted Exhibit A which provided data showing that treatment of a dog with a combination of a gene encoding Factor IX and cyclophosphamide blocked formation of anti-canine Factor IX antibodies resulting in sustained expression of Factor IX levels sufficient for partial correction of coagulation.

On February 3, 2003, the Examiner issued an Advisory Action indicating that the claims as amended required further consideration and search. In response, Applicants filed the first Request for Continued Examination in this Application requesting entry and consideration of the amendment after final.

Examiner Whiteman issued a non-final rejection of the claims on January 9<sup>th</sup>, 2004. Notably, the \$112, first paragraph rejection of the claims was **withdrawn** in view of the evidence presented in Exhibit A. Several new rejections were made under \$103 based on the combination of US Patent 6,372,208 to Wilson et al., Bach et al., Tripathy et al., Nilsson et al. and Warriar et al. In response Applicants argued that the prior art did not teach each and every element of the claimed invention, and therefore the instant method could not be considered obvious. Notably, the primary reference relied on for the rejection of claims 1-3, 4, 6, 10, 12-16, 19, 20, 28-33, 35, 37, 38 and 40 cited was the '208 patent to Wilson et al. This patent is directed to a method of reducing an immune response to a viral vector containing a selected transgene via administration of an immune modulator

which inhibits an immune response to the viral vector. Clearly, the USPTO has taken the position that delivery of a transgene to a mammal via gene therapy was enabled and known in the art at least as early as April 16, 2002, which is the issue date of the Wilson patent.

On July 29, 2004, Examiner Whiteman maintained the rejections of all the claims under §103. Again, Applicants are confounded as to how the USPTO can assert for over 4 years that the present invention is obvious and now, after 9 years of prosecution assert that the claimed method is inadequately enabled.

Applicants filed the second Request for Continued Examination in this application on January 31, 2005 and conducted a second telephonic interview. In response, a new non-final rejection dated July 5, 2005 was issued by Examiner Whiteman. In this paper, the Examiner rejected certain claims under 35 U.S.C. §112, second paragraph for omitting essential steps and maintained all of the above-noted §103 rejections based on the '208 patent to Wilson as the primary reference. In response, Applicants reiterated that the cited prior art was concerned primarily with reducing the immune response to the vector used to deliver the therapeutic protein rather than the therapeutic protein per se.

On April 24, 2006, Examiner Whiteman issued another non-final rejection. In this paper, the Examiner did not maintain any of the aforementioned rejections under 35 U.S.C. §103 or 112, second paragraph but rather raised a new rejection under §102(e) based on US Patent 6,929,796 to Conti-Fine. The Examiner also raised new rejection under §103 based on the combination of the newly cited Conti-Fine patent and the Wilson patent.

Applicants responded on October 23, 2006. The rejection under §102(e) was overcome by limiting the claims to the use of cyclophosphamide only. Applicants also presented arguments that the combination of Conti-Fine with Wilson failed to place

each of the elements of the presently claimed method in the public domain and thus the Examiner had failed to establish a prima facie case of obviousness.

Examiner Whiteman mailed out yet another final rejection on January 11, 2007 maintaining the §103 rejection over the combination of Conti-Fine and Wilson and raising a new rejection based on the combination of Conti-Fine, Wilson et al. and the previously cited Trapnell et al.

In response, Applicants filed the third Request for Continued Examination in this application on June 11, 2007, limiting the claims to the subject matter previously indicated as enabled by the Examiner and including features which distinguished them from the cited prior art, i.e., a method for preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated vector, said method further comprising administration of cyclophosphamide prior to, or concomitantly with the administration of the viral vector. Apparently, Applicants arguments were effective to overcome all of the outstanding art rejections as none of these were maintained in the Action dated February 28, 2008. Indeed, Applicants fully expected to receive a Notice of Allowance in response to the June 11, 2007 submission.

In the non-final action dated February 26, 2008, Applicants were notified that the Examiner for this case had been changed and that Dr. Singh was now assigned to this application. Examiner Singh, quite unexpectedly, rejected all of the pending claims under 35 U.S.C. §112, first paragraph. As mentioned above, this rejection seems highly inappropriate as Examiner Whiteman has stated on the record not once, but twice, exactly what the specification enables. Inasmuch as the claims were amended to reflect this scope, Applicants submit the present rejection under 35 U.S.C. 112, first paragraph is inappropriate and should be withdrawn.

Applicants also take exception to certain assertions made

by Examiner Singh in the February 26, 2008 Official Action. Specifically, at page 3 of that Action, the Examiner states the following: "It is noted that although instant claims are directed to a method of preventing formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated vector, they have been analyzed for their intended effect of **correcting** hemophilia B in any mammal including humans by delivering to any site and any dose of AAV comprising Factor IX." Applicants strenuously object to the Examiner's requirement that the present method be effective to **correct** hemophilia B. Clearly, the method requires only that the transgene be expressed in the mammal at levels sufficient to induce the formation of inhibitory antibodies to Factor IX. Contrary to the Examiner's assertion, **correction** of the hemophilia B phenotype is not required by these claims.

In support of his contention that gene therapy is unpredictable, the Examiner cites several studies (most being conducted well after applicants filing date) on page 6 of the February 26, 2008 Official Action indicating that variability is observed in expression levels in different studies using different routes of administration different viral doses and different animal models. However, in each study, Applicants note production of the transgene was observed. Inasmuch as the presence of a non-self protein in an animal provokes an immune response, Applicants submit that the art relied on by the Examiner supports Applicants contention that the claims are fully enabled by the disclosure in the specification.

The Examiner also states that the data presented in the application cannot be extrapolated to other mammalian species. This statement is confounding to Applicants. Applicants have demonstrated operability of the method in rodents and canines. Additional studies describe results in non-human primates. Indeed, Jiang et al. (made of record in Applicants previous response) provides results from a phase I clinical trial which clearly demonstrates that AAV is effective to deliver Factor



IX to humans.

In the response filed on 26 August 2008, Applicants provided several cogent arguments refuting the Examiner's position regarding enablement and questioned the propriety of the Examiner's requirement that the claimed method result in a correction of hemophilia B rather than an inhibition in the formation of inhibitory antibodies specific for Factor IX produced following delivery to a mammal using an AAV vector.

**CLAIMS 1, 2, 24, 28, AND 43-46 SATISFY THE ENABLEMENT  
REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH**

In the Final Official Action dated June 2, 2009, the Examiner has maintained the rejection of claims 1, 2, 24, 28 and 43-44 under 35 U.S.C. §112, first paragraph. Specifically, the Examiner contends that because gene therapy is unpredictable, undue experimentation is required to practice the claimed method.

Claim 43 has been amended to recite that production of Factor IX in said mammal induces formation of inhibitory antibodies that are optionally determined by Bethesda titers. Support this amendment can be found in claim 12 in the application as filed, and at page 13, line 20 wherein antibody levels were also determined via Western blot.

The Examiner again relies on Walsh et al. who teach that different routes of administration of AAV vector can result in variable expression levels. However, as mentioned previously, in each case expression of the transgene **was** observed. Thus, non-self antigen (e.g., Factor IX) which is known to induce formation of inhibitory antibodies, was present. Nothing more is required under 35 U.S.C. §112, first paragraph to render the invention operable as claimed.

Applicants also note the claims encompass the use of cyclophosphamide as the immunosuppressive agent. Cyclophosphamide has been in use clinically for decades. The

skilled clinician can readily determine the appropriate dosage of cyclophosphamide effective to inhibit antibody production based the weight of the patient without resorting to undue experimentation.

Applicants strenuously object to the statement at page 4 of the Official Action wherein MPEP 2164.05(a) is cited for the premise that if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing. Frankly, none of the references cited by the Examiner take the position that gene therapy is not possible, nor does the USPTO. A search of the USPTO database using ACLM/"gene therapy" reveals no less than 263 issued patents encompassing compositions and methods for performing gene therapy (copy of titles of first 100 patents attached). Prior art discussed above, and cited against the presently claimed method, including US Patent 6,093,392 to Dr. High clearly indicate that as of the filing date, delivery of Factor IX via an AAV vector was enabled and effective to produce Factor IX in mammals lacking the same.

At page 4, the Examiner notes (citing work of one of the present co-inventors) that the art teaches that dose of vector and level of transgene expression may determine whether antibodies are transient or persistent. Thus, the Examiner (and the art) are clear that regardless of route or dose, inhibitory antibodies are produced.

Applicants also object to the characterization of Jiang et al. at page 6 of the official action wherein the Examiner states that the data presented in Jiang et al. is premature and "not fully resolved even several years after the filing of this application". Applicants submit that Jiang et al. report that every patient treated with the AAV-FIX vector exhibited FIX expression. Applicants reiterate that expression of a non-self protein is sufficient to provoke an immune response. Nothing further is required by the claimed method.

Regarding the teachings in Walsh et al., the section cited by the Examiner (bottom of page 1001 over to page 1002) again supports Applicants' position. In each case, transgene expression was observed, thus providing conditions suitable for inducing an unwanted antibody response. Notably, Walsh et al. conclude with the following statement: Hemophilia gene transfer represents a combination of vector delivery systems, animal models and clinical studies designed to answer specific questions. Not only will these studies benefit hemophilic patients but should also instruct others in the field as well. Thus, even Walsh believes that genetic correction of hemophilia is feasible.

At page 9 of the Official Action, the Examiner relies on Ponder for the premise that different AAV serotypes give rise to differing levels of expression of the transgene. However once again, although expression varied, production of Factor IX was measurable. Thus, other serotypes of AAV are clearly able to transduce target cells and give rise to Factor IX production which may give rise to an unwanted inhibitory antibody response. It is a purpose of the present method to inhibit the formation of such antibodies.

At page 10, the Examiner again reiterates that he is reading the requirement of correcting hemophilia B into the claimed invention. Applicants submit that this requirement is inappropriate and erroneous. Indeed, in each of the studies relied on by this and the previous Examiner, introduction of a transgene encoding Factor IX using AAV vectors of different serotypes and administered via different routes resulted transgene expression in the treated mammal, albeit at different levels. Such expression would give rise to an undesirable immune response which can be inhibited by concomitant administration of an immunosuppressive agent such as cyclophosphamide. In view of all the foregoing, Applicants submit that the specification fully enables the presently claimed method. Accordingly, the rejection of claims 1, 2,

24, 28, 43 and 44 under 35 U.S.C. §112, first paragraph is untenable and should be withdrawn.

#### CONCLUSION

It is respectfully requested that the amendments presented herewith be entered in this application. The amendment to claim 43 and accompanying remarks are believed to clearly place the pending claims in condition for allowance. The claims as presently amended are also believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case. Therefore, it is respectfully urged that the rejections set forth in the June 2, 2009, Official Action be withdrawn and that this application be passed to issue.

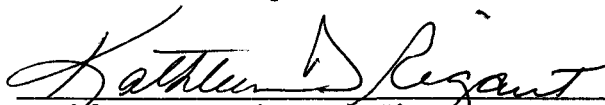
Given the lengthy prosecution of this Application, the Examiner is respectfully requested to contact to the undersigned prior to issuing another paper in this application to discuss any issues that remain after this response has been fully considered.

If a fee is required or an overpayment is made, the Commissioner is authorized to charge or credit the deposit account of the undersigned, Account No. 04-1406.

Early and favorable action on the present application is earnestly solicited.

Respectfully submitted,  
DANN, DORFMAN, HERRELL AND SKILLMAN  
A Professional Corporation

By

  
Kathleen D. Rigaut, Ph.D.  
PTO Registration No. 43,047

Telephone: (215) 563-4100

Facsimile: (215) 563-4044

Email: krigaut@ddhs.com

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| 10 7,521,239 | <a href="#">Photochemical internalization for virus-mediated molecule delivery into the cytosol</a>                                   |
| 11 7,515,954 | <a href="#">Non-contact cardiac mapping, including moving catheter and multi-beat integration</a>                                     |
| 12 7,510,699 | <a href="#">In vivo fluorescence sensors, systems, and related methods operating in conjunction with fluorescent analytes</a>         |
| 13 7,505,810 | <a href="#">Non-contact cardiac mapping, including preprocessing</a>  |
| 14 7,500,970 | <a href="#">Catheter drug delivery system and method for use</a>  |
| 15 7,498,314 | <a href="#">Expression vectors and uses thereof</a>   |
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| 17 7,494,802 | <a href="#">Amniotic membrane covering for a tissue surface and devices facilitating fastening of</a>                                 |

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49 [7,282,578](#) **T** [Nucleic acid molecule comprising a nucleic acid sequence which codes for a haemocyanin](#)

50 7,282,489 **T** Compositions and methods for performing reverse gene therapy

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